UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/864,451	05/25/2001	Louis D. Falo JR.	076333-0267	3388

22428 7590 02/19/2004

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/19/2004

SoK

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/864,451	FALO ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 25-36* is/are pending in the application.

4a) Of the above claim(s) *25-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I, Claims 1-12, filed 11/20/03, without traverse, is acknowledged.

2. Claims 25-36 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-12 are pending.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because, uninitialed changes in the residence address of Inventor Falo have been made.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed formulations would comprise effective formulations for prophylactic and therapeutic anti-tumor and anti-viral immunization.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding a formulation comprising a dendritic cell (DC) hybridoma which provides anti-tumor and anti-viral immunity, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable. The state of the medical art is such that no formulations comprising a DC hybridoma which induces either effective anti-tumor or anti-virally-infected cell CTL-dependent immunity are known in the art. Also note that the *only* intended uses of the formulations of the claims are for *in vivo* therapy, i.e., the prevention or treatment of disease. Accordingly, the disclosure must be enabling for *in vivo* use of the claimed formulations.

Regarding the claimed formulations and pharmaceutical compositions, it is noted that the specification discloses two relevant Examples; in Example 5 tumor immunity is demonstrated in a mouse model and in Example 6 regression of an existing tumor is disclosed, also in a mouse model. This disclosure is, however, insufficient to enable the formulations of the claims. It is well-known in the cancer research field that eminent researcher Judah Folkman has been often quoted saying "I can cure cancer - in a mouse." The point is that results achieved in mouse models often correlate poorly with those achieved in humans. As disclosed in the specification at page 2, the instant formulations would take advantage of the belief that tumor cells express a set of tumor-specific antigens (referred to as tumor associated antigens (TAAs) in the art) which can be recognized by CTLs. Unfortunately, positive results achieved versus TAAs in animal models do not generally correlate with positive results in humans. As taught by Bodey et al. (2000) the reasons are relatively straight-forward:

"The theoretical basis for all of these approaches [immunotherapy] is very well founded. Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained within the cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor; through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use."

Indeed this selection for the most aggressive tumor cells would likely exacerbate disease in the long run. It is noted that none of the experiments disclosed in the specification extend beyond 2 or 3 months, thus this likely exacerbation of disease cannot be seen in the examples. The reference also teaches that in one cancer model, "hyperstimulation" with a genetically modified tumor cell that provided both IL-2 and costimulatory molecules (much as the formulations of the instant claims might), "adverse effects on tumor immunity" were seen. The reference then teaches that the "mechanism [of the adverse effect] is not yet completely understood." Clearly then, if formulations for achieving immunospecific CTL responses against tumors did not work in humans, and were not understood, in 2000, they were at best, highly unpredictable in 1997 (the priority date of the instant application).

Regarding formulations which induce effective anti-virally infected cell immunity, even less is known. Indeed, as taught by Cohen (2002) it is not yet even known whether a CTL response against a virus such as HIV is even technically capable of providing effective immunity.

The specification provides no data to enable claims drawn to a DC hybridoma which induces effective anti-virally-infected cell immunity. Note that the specification discloses background references and examples that deal exclusively with anti-tumor DC responses and anti-tumor DC hybridomas. Anti-virally-infected cell immunity is disclosed only in concept, a concept that clearly was not enabled in 1997.

In the case of HIV infection the situation is even more unpredictable given the fact that both DCs and T cells are infected by the virus. As taught by Frank et al. (2002):

"A dendritic cell (DC) encountering an immunodeficiency virus should pose a threat to the virus, by efficiently processing and presenting viral antigenic determinants to activate specific anti-viral T and B cell immunity. While this may occur *in vivo*, it is apparent that DC-entrapped viruses can freely spread between cells, move to distal tissues, and proliferate rapidly particularly upon meeting CD4+ T cells. In fact, the latter is further augmented when the T cells are activated. Thus, it seems that immunodeficiency viruses exploit the unique ability of DCs to survey the periphery and capture incoming pathogens, traffic around the body often targeting the lymphoid tissues, and efficiently communicate with naive and memory T cells. Combined with the fact that DCs are likely the first leukocytes interacting with virions crossing the mucosae, these features provide the basis on which the virus maximizes its chance to establish infection even in the face of immune activation."

Given this teaching, it would seem then that the formulations of the instant claims would be more likely to exacerbate viral infections than to treat or prevent them. The reference further teaches that other viruses, including herpes simplex virus, measles virus, sendai virus, vaccinia virus, and cytomegalovirus infect DCS and down-modulate their antigen presenting functions. Accordingly, the use of the DC hybridomas of the instant claims to induce effective anti-virally-infected cell immunity would be highly unpredictable. Said unpredictability would then require undue experimentation in using the formulations of the instant claims *in vivo* as disclosed in the specification.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the

lack of sufficient working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-3 and 5-6 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Peters (1981).

Peters teaches a formulation comprising a hybridoma having a first DC fused to a sarcoma cell (see entire document). Note that the source of the DC cell is irrelevant to the claim absent a showing that said source *is* relevant. Further note[6] that while the reference does not indicate the ratio of DCs to tumor cells in the formulation, if the ration did not fall within the 2 to 4 log range of the claims, it is highly unlikely that the author would have been able to purify and analyze the properties of the product.

The reference clearly anticipates the claimed invention.

8. Claims 1-3, 5-8, and 10-12 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by WO 96/30030.

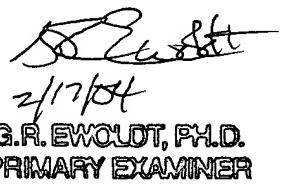
WO 96/30030 teaches a formulation and pharmaceutical composition comprising a hybridoma having a first DC from a culture of precursors (see particularly page 12, last paragraph - page 13, first paragraph) and a sarcoma cell (see particularly Example 9). The reference further teaches a ratio of DC:tumor of about 1:100-100:1, 1:10-10:1, and 6:1 (see particularly Examples 3 and 9).

The reference clearly anticipates the claimed invention.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

Please Note: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600